Remarks:

Reconsideration of the application in view of the above amendments and following remarks is requested. Claims 1-3 and 9-11 and 18-20 are now in the case. Claims 1 and 9 have been amended. Support for these amendments can be found at least in the claims as filed. Claims 18-21 are newly added. Support for these claims can be found at least in Example 5 of the specification as filed as well as page 10, line 30 – page 11, line 5. Claims 4-8 and 12-17 have been canceled. Applicants assert that the present amendment adds no new matter. Applicants reserve the right to prosecute claims to cancelled subject matter in one or more continuing applications.

The abstract of the disclosure is objected to because it does not disclose the claimed invention (aka the polypeptide of claim 1). A new abstract has been provided that addresses the Examiner's concerns.

Claims 1, 2-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner's comments pointed to two specific aspects of the claims which allegedly did not comply with the written description requirement: the full scope of the trimerizing proteins and the full scope of the claimed TACI proteins. Although Applicants do not agree with these findings, in order to speed prosecution, the language "trimerizing proteins" without further limitation has been deleted from the claims as amended, thus overcoming the Examiner's concern about this terminology. As for the full scope of TACI proteins, it is respectfully submitted that at the time of filing of this application, the sequence of the TACI protein for many species was well known in the art (see, for example von Bulow et al., Mamm. Genom. 11, 628-632 (2000), copy attached). This contrasts starkly with the status of insulin cDNA sequence at the time of filing of the application which was at issue in the Eli Lily litigation. Furthermore, it would have been well within the purview of one of ordinary skill to identify the TACI sequences of other species using hybridization techniques. As such, it is respectfully submitted that the written description rejection of these claims is without basis, and is correctly withdrawn.

Claims 1, 2 are rejected under 35 U.S.C 102(e) as being anticipated by Ashkenazi eti al. (US 2006/0073146). Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ashkenazi et al. (US2006/0073146) in view of Rixon et al. (US 2003/0103986). Claims 1, 2, 4, 5 are rejected under 35 U.S.C. 103(a) as being

unpatentable over Ashkenazi et al. (US 2006/0073146) in view of Seol et al. (US 2002/0128438) in view of Frischholz et al. and claims 3, 6, and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ashkenazi et al. (US 2006/0073146) in view of Seol et al. (US 2002/0128438) in view of Frischholz et al. as applied to claims 1, 2, 3, 5 above, and further in view of Rixon et al. (US 2003/0103986). Applicants respectfully traverse these rejections based on these prior art teachings.

Specifically, the claims have been amended to recite a trimerizing fragment of Heat Shock Protein-1. Neither this protein, nor the the trimerizing function of fragments of this protein have been disclosed in the cited art. As such, it is respectfully submitted that the claims as amended overcome the outstanding rejections.

On the basis of the above amendments and remarks, Applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6752.

It is believed that no fee is due. However, in the event that a fee is due, please charge any fee or credit any overpayment to Deposit Account No. 26-0290.

Respectfully Submitted,

Michelle L Lewis

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Enclosures:
von Bulow et al.
Petition and Fee for Extension of Time

Customer No. 10117
ZymoGenetics, Inc.

Mammalian Genome 11, 628–632 (2000).
DOI: 10.1007/s003350010125

Mammalian Genome
Incorporating Mouse Genome

Molecular cloning and functional characterization of murine Transmembrane Activator and CAML Interactor (TACI) with chromosomal localization in human and mouse

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Received: 9 November 1999 / Accepted: 27 March 2000

Abstract. The human Taci gene (Transmembrane Activator and CAML Interactor) encodes a recently discovered member of the Tumor Necrosis Factor Receptor family. TACI is expressed in B-lymphocytes and may act to regulate humoral immunity. To identify functionally important regions of the protein, we have isolated and characterized the murine homolog of the human Taci cDNA. The proteins display 61.5% similarity and 54.6% identity. Mouse TACI is a type III transmembrane protein, as judged by the lack of a cleaved signal sequence and its N-terminal extracellular exposure. The intracellular domains of the mouse and human proteins share a single, defined region of high sequence conservation (19 of 23 residues identical). This constitutes a novel domain that may play a part in the initiation of signal transduction through TACI. In support of this notion, mouse TACI was found to activate NFAT, NFkB, and AP1 transcription factors in a transient transfection assay. The Taci gene was localized to human Chromosome (Chr) 17p11 by fluorescence in situ hybridization. The murine homolog was localized by intraspecific backcross analysis to the middle of Chr 11, a region that is syntenic to human Chr 17p. This work identifies conserved domains within TACI that may mediate the cellular distribution and signal transduction function of the protein and extend the details of homology between mouse Chr 11 and human 17p.

Introduction

Cell surface receptors of the Tumor Necrosis Factor (TNF) superfamily are involved in a number of responses by immunological cells. These include the regulation of clonal selection by apoptosis (Ashkenazi and Dixit 1999) as well as acting as costimulatory receptors in concert with the T-cell (Hintzen et al. 1994) and B-cell receptors (Laman et al. 1996). Transmembrane Activator and CAML Interactor (TACI) is a recent addition to this family of receptors and was cloned by virtue of its association with the CAML protein (Calcium-Modulating Cyclophilin Ligand; Bram and Crabtree 1994) in a yeast two-hybrid interaction screen. We previously demonstrated that the TACI protein, when ectopically expressed in Jurkat T cells and cross-linked with a TACI antibody, could activate calcium-dependent transcription factors (such as NFAT) apparently through a physical interaction with the CAML protein. Furthermore, TACI could also activate AP-1- and NFkB-specific transcription in a manner independent of CAML (von Bülow and Bram 1997).

Several novel features of the human TACI protein were noted previously, but their significance was not clear. Firstly, the C-terminal cytoplasmic domain of TACI bears no sequence similarity to known activators of NFAT or NFkB. Thus, it was unclear which residues activate signal transduction cascades within the cell. Secondly, TACI appeared to be a type III single transmembrane protein owing to its extracellular N-terminal exposure in the absence of an N-terminal cleaved signal sequence (Harley and Tipper 1996). This topology is unique among known TNFR family members to date and might represent an important new mechanism by which receptor function is regulated. To determine which features of the protein might have functional significance as demonstrated by evolutionary conservation, we have isolated and characterized the mouse homolog.

Materials and methods

cDNA library screening and constructs. The mouse Taci cDNA clone was derived by low-stringency hybridization from a murine spleen cDNA library in Lambda Zap II (Stratagene Cloning Systems, La Jolla, Calif.) by standard protocols (Sambrook et al. 1989). The probe was a 899-bp *NotI/ApaI* fragment derived from full-length human Taci cDNA in pBluescript (pSK-hTACI), and contained the entire open reading frame. The resulting mouse *Taci* cDNA-containing plasmid (named pSK-mTACI) was excised from phage with Exassist (Stratagene) and the insert sequenced by using dye-termination chemistry. To facilitate the construction of an expression plasmid, we amplified the open reading frame of mouse *Taci* cDNA by PCR with Pfu polymerase (Stratagene) from pSK-mTACI, using oligodeoxynucleotides that introduced *Eco*RI and *Bgl*II sites on the respective 5′ and 3′ ends of the PCR product. The *Eco*RI- and *Bgl*II-digested product was then ligated into a modified form of the pBJ5 expression vector (pFLEX) such that N-terminal FLAG-tagged mouse *Taci* expression would be driven off the SRα promoter when transfected into mammalian cells. The expected expression of the Flag-tagged mouse Taci protein was confirmed by transfection of 293T cells with pFL-mTACI by using Superfect (Qiagen Inc., Valencia, Calif.) and Western blot with standard protocols, probing with the M2 anti-Flag monoclonal antibody (not shown). To show that mTACI is expressed with an extracellular N-terminus, pFL-mTACI (2 μg) was co-electroporated into TAg Jurkat cells (Northrop et al. 1993) with a plasmid which directs expression of murine CD8a (ACT-LYT, 2 μg; Bram and Crabtree 1994). After 48 h incubation in RPMI with 10% FCS at 37°C in a humidified incubator with 5% CO_2, cells were stained with the M2 anti-Flag antibody (Sigma Chemical Company, St Louis, Mo.) followed by FITC-conjugated goat anti-mouse IgG (Jackson ImmunoResearch Laboratories Inc., West Grove, Pa.), and with phycoerythrin-conjugated rat anti-murine CD8a (PharMingen, San Diego, Calif.). Cells

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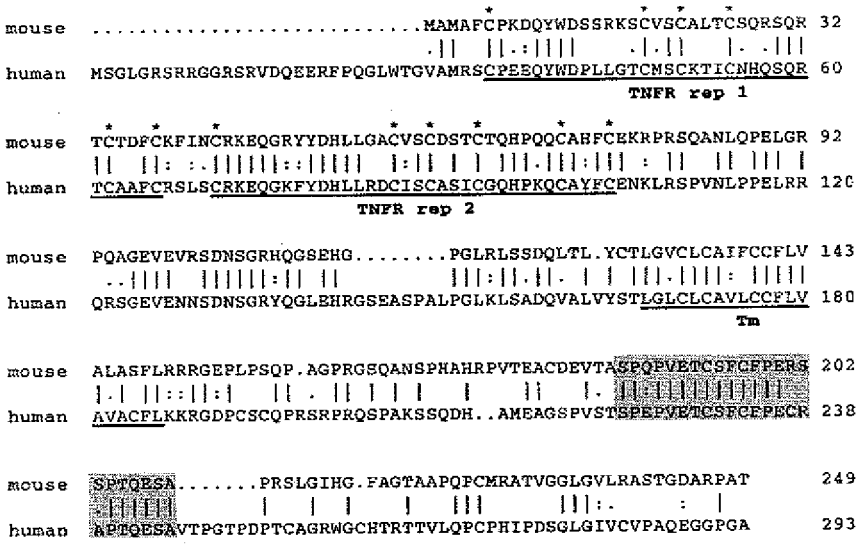


Fig. 1. Alignment of the conceptually translated products of the human and murine Taci cDNAs using the GAPS algorithm of the GCG suite (Wisconsin Package Version 10.0). The two TNFR repeat motifs and the transmembrane segment (Tm) are underlined, the conserved cytoplasmic sequence is shaded, and asterisks denote the conserved cystine residues within the TNFR repeats.

were then incubated with propidium iodide (PI) and analyzed by flow cytometry. Gating was performed to exclude PI-positive (dead) cells, include PE-positive (transfected) cells, and analyze FITC (TACI) staining.

Reporter assays. To determine activity of NFAT, AP-1, and NFkB, appropriate reporter constructs for these transcription factors (Bram et al. 1993) were electroporated into TAg Jurkat cells together with either pFL-mTACI or empty vector. Cells were electroporated with 2 μg pFL-mTACI or empty vector with either 6 μg SXNFAT (NF-AT), 2 μg MAP-SEAP (AP-1), or 1 μg SXNFkB (NFkB) per 10^7 cells at 250V and 960 μF. Following electroporation, cells were diluted into RPMI with 10% FCS and incubated overnight at 37°C in a humidified incubator with 5% CO_2. Cells were then stimulated with the indicated antibodies and drugs and then incubated for a further 24 h to allow production of the secreted alkaline phosphatase (SEAP) reporter. SEAP activity was determined as previously described (von Bülow and Bram 1997). Antibody stimulation of mTACI was achieved by cross-linking the FLAG epitope with M2 monoclonal antibody (0.2 μg/ml final) immobilized on goat anti-rat IgG magnetic beads (with a twofold excess of beads for the amount of antibody). Data for each transfection were normalized, with the response achieved by stimulation of the cells with PMA (25 ng/ml) and ionomycin (1 μM).

Fluorescence in situ hybridization. Two synthetic oligodeoxynucleotides with sequences corresponding to residues 242–262 (AAGTTCTATGACCATCTCCTG) and antisense 384–405 (TCTGAATTGTTTTCAACTTCTC) from the human Taci cDNA sequence were prepared. This primer pair was used in a polymerase chain reaction with human genomic DNA as template, and the predicted 164-bp DNA fragment was derived (not shown). A human genomic DNA library (Du Pont Merck Pharmaceutical Co., human foreskin fibroblast P1 library-DMPC-HFF#1) was screened by PCR with the above primers (Genome Systems Inc., St Louis, Mo.), and two independent clones from the Taci locus were isolated (DMPC-HFF#1-768-G8 and DMPC-HFF#1-900-G8). DNAs from these P1 clones were labeled with digoxygenin-11-dUTP by nick translation. The labeled probes were combined with sheared human DNA and hybridized to normal metaphase chromosomes in 50% formamide, 10% dextran sulfate, and 2× SSC. Specific hybridization signals were detected with fluorescein-conjugated sheep antibodies to digoxygenin. Chromosomal assignment was confirmed by cohybridization of both clones with biotinylated Chr 17 centromere-specific probe D17Z1 (Oncor Inc., Gaithersburg, Md.) and treatment of the slides with Texas red avidin.

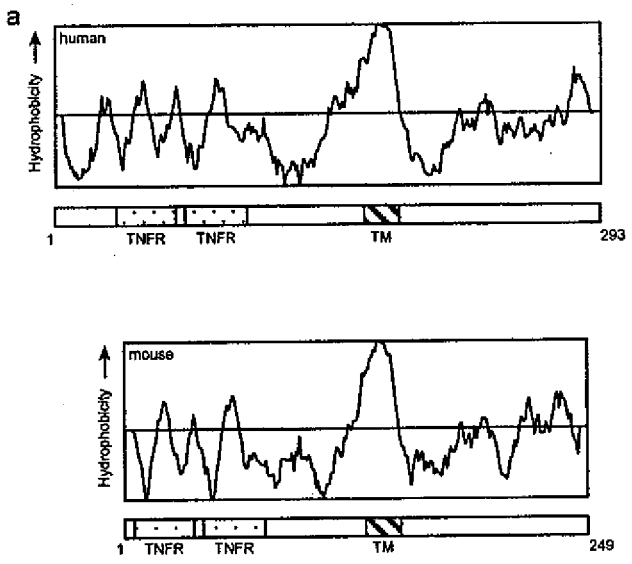
Interspecific mouse backcross mapping. Interspecific backcross progeny were generated by mating (C57BL/6J × *M. spretus*) F_1 females and C57BL/6J males as described (Copeland and Jenkins 1991). A total of 205 N_2 mice were used to map the *Taci* locus (see Results for details). DNA isolation, restriction enzyme digestion, agarose gel electrophoresis, Southern blot transfer, and hybridization were performed essentially as described (Jenkins et al. 1982). All blots were prepared with Hybond-N^+ nylon membrane (Amersham Pharmacia Biotech, Piscataway, N.J.). The probe, a 1312-bp *Eco*RI fragment of mouse cDNA, was labeled with [α^{32}P] dCTP with a nick translation labeling kit (Roche Molecular Biochemicals, Indianapolis, Ind.); washing was done to a final stringency of 1.0 × SSCP, 0.1% SDS, 65°C. Fragments of 8.1, 7.4, and 1.7 kb were detected in *Hin*cII-digested C57BL/6J DNA, and fragments of 8.1, 7.4, 1.7 and 1.0 kb were detected in *Hin*cII-digested *M. spretus* DNA. The presence or absence of the 1.0-kb *Hin*cII *M. spretus*-specific fragment was followed in backcross mice.

A description of the probes and RFLPs for the loci linked to *Taci* including *Il13*, *Kcnj2*, and *Myhsf1* has been reported previously (McKenzie et al. 1993; Takumi et al. 1996). Recombination distances were calculated by using Map Manager, version 2.6.5. Gene order was determined by minimizing the number of recombination events required to explain the allele distribution patterns.

Results and Discussion

Isolation and expression of the murine Taci cDNA. The full coding sequence of human Taci cDNA was used as a probe to isolate the corresponding murine sequence from a mouse spleen cDNA library. By using low stringency, 10^6 individual clones were screened with the human probe, and four identical positive clones were isolated. The DNA sequences were determined and compared with the human Taci gene. The 1439-bp insert was 51% identical to human Taci cDNA and contained an open reading frame with an in-frame stop codon upstream of the first ATG. From this analysis, we conclude that this clone includes the entire reading frame of murine *Taci*.

A comparison of the deduced amino acid sequences of human and murine Taci open reading frames using the gap algorithm from the GCG suite (Wisconsin Package Version 10.0) (Fig. 1) revealed that human and murine TACI shared 61.5% similarity and 54.6% identity. Like human TACI, murine TACI has a pair of cystine-rich TNFR repeats within the N-terminal half of the protein. These domains define the TNFR superfamily. In the case of TNFR1, each domain forms a specific, folded structure stabilized by disulfide bonds (Banner et al. 1993). Within the cystine-rich domain of human and mouse TACI, the positions of the cystine residues are strictly conserved, implying that these proteins would have a similar secondary structure on the extracellular surface of cells. A further area of conserved sequence homology is a cytoplasmic region between residues 186 and 209 in mouse TACI. This region shares 83% homology (19 of 23 residues, shaded area of Fig. 1) with human TACI, compared with 32% homology for the remainder of the intracellular domain. This striking sequence conserva-



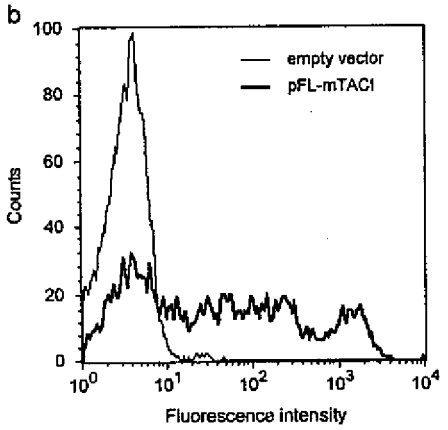


Fig. 2. (a) Kyte-Doolittle hydrophobicity plots of human and mouse TACI peptides (Geneworks, Oxford Molecular Group). (b) Flow cytometry showing extracellular exposure of an N-terminal FLAG-tagged expression construct of murine *Taci*. Jurkat cells expressing the SV40 large T antigen (Northrop; Ullman et al. 1993) (TAg) were electroporated with either the Flag-mouse TACI construct (thick line) or an empty vector control (thin line), together with a murine cd8a expression plasmid. Intact transfected cells were gated by the expression of murine CD8a, stained with phycoerythrin-conjugated rat anti-mouse CD8a antibodies. Shown is binding of M2 anti-Flag antibodies counterstained with FITC-conjugated goat anti-mouse IgG.

tion advocates an important role for this region, perhaps in the activation of the NF-kB, AP1, or NFAT transcription factors.

We previously raised the possibility that TACI is a type III transmembrane protein because it appeared to be oriented with its amino-terminus in the extracellular compartment but lacked a cleaved signal sequence. Members of this rare protein class insert into lipid bilayers by an unknown mechanism. Because most type III transmembrane proteins have shorter extracellular domains than does TACI, it was not clear whether it was indeed a true member of this family or if, instead, an incomplete cDNA clone had been obtained from the human cDNA library previously. Our current identification and analysis of the mouse homolog verified that this unusual configuration is indeed present in the TACI gene

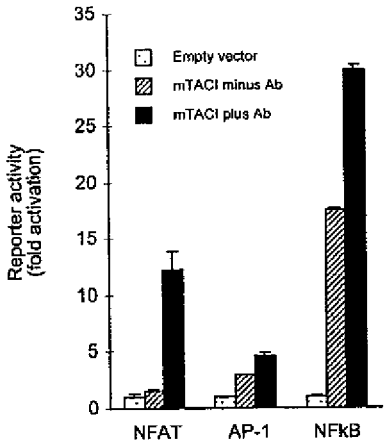


Fig. 3. Activation of NFAT-, AP-1-, and NFkB-specific transcription by murine TACI. TAg Jurkat cells were electroporated with either empty vector or the N-terminal Flag-tagged mouse TACI expression plasmid together with reporter constructs for either NFAT, AP-1, or NFkB driving the expression of secreted alkaline phosphatase (Bram, Hung et al. 1993). Cells were then incubated with goat anti-mouse IgG-conjugated beads as controls, or beads coated with anti-Flag monoclonal antibodies to cross-link TACI. Reporter activity was assayed as described, using maximal stimulation with PMA and ionomycin to normalize expression (von Bülow and Bram 1997).

and appears to have been conserved throughout evolution. It is tempting to speculate that translocation of the TACI amino-terminus to the cell exterior may provide a level of regulation for expression and function of the protein, not unlike that proposed for cell-surface exposure of FAS (Bennett et al. 1998).

A kyte-Doolittle hydrophobicity analysis (Geneworks, Oxford Molecular Group, Campbell, Calif.) predicted that murine TACI, like human TACI, is also a single transmembrane protein with no N-terminal hydrophobic signal sequence (Fig. 2a). Ectopic expression of an N-terminal FLAG-tagged mTACI expression construct in Jurkat cells revealed extracellular exposure of the N-terminal FLAG epitope (Fig. 2b), confirming that murine TAIC shares the same surface topology with human TACI, i.e., a type 3 membrane protein that has an extracellulary exposed N-terminus in the absence of an N-terminal cleaved signal sequence.

To confirm the functional authenticity of mouse TACI, we performed reporter assays for the transcription factors NF-AT, AP-1, and NFkB, which are known to be activated by cross-linked human TACI in the same assay system (von Bülow and Bram 1997). We transfected the expression plasmid PFL-mTACI into TAg Jurkat cells together with reporters for either NF-AT, AP-1, or NFkB driving the expression of secreted alkaline phosphatase (SEAP). Reporter expression was determined in the presence and absence of cross-linked anti-FLAG antibodies. Like human TACI, mouse TACI is able to activate all three of the tested reporters, which were increased by the addition of cross-linking antibodies (Fig. 3). The activation of NFAT was also dependent on calcineurin, as evidenced by the depletion of the NFAT response to mTACI in the presence of cyclosporin A (not shown).

Chromosomal localization of the human and murine Taci loci. The chromosomal localization of the human Taci locus was performed by fluorescence in-situ hybridization (FISH). Tow genomic P1 clones were derived by screening a human genomic library with PCR primers, which amplified a Taci-specific sequence from human genomic DNA. These clones were labeled with digoxygenin and hybridized to normal metaphase chromosomes derived from peripheral blood lymphocytes stimulated with phytohemagglutinin (PHA). Specific hybridization signals were detected with fluorescein-conjugated sheep antibodies to digoxy-

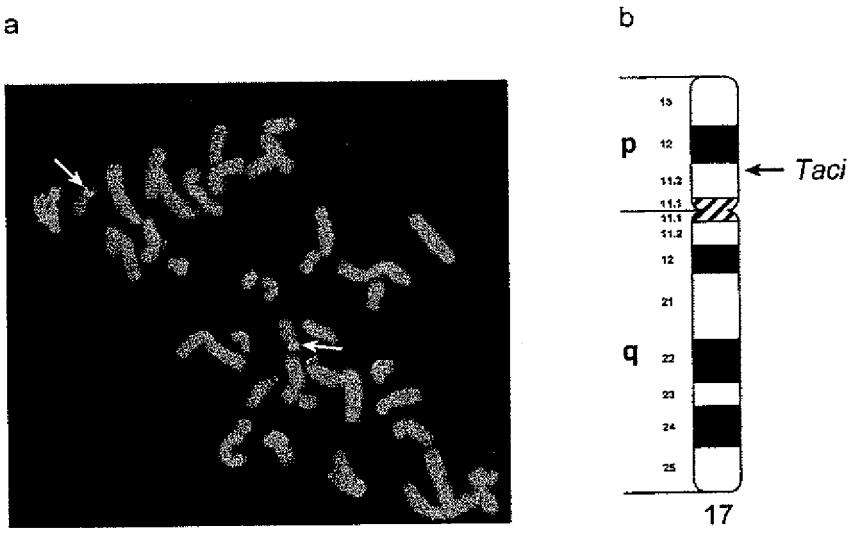


Fig. 4. Localization of the human Taci gene to Chr 17. (a), Taci-specific hybridization (arrows) is shown by the green (FITC) staining and the Chr 17 centromere by red (Texas Red). Chromosomes were counterstained with DAPI. (b), Ideogram depicting localization of the human Taci locus to 17p11 (arrow).

genin. The cells were then counterstained with DAPI and analyzed by microscopy. These experiments resulted in the specific labeling of the short arm of a group E chromosome, which was believed to be Chr 17 on the basis of the DAPI banding. Definitive chromosomal assignment was confirmed by cohybridization of both clones with a biotinylated Chr 17 centromere-specific probe followed by incubation with Texas red avidin. Band assignment for both clones was made by fractional length measurements on a total of eight specifically hybridized Chr 17. These data indicated that the clones are located on a position which is 30% of the distance from centromere to the telomere of Chr arm 17, an area that corresponds to 17p11 (Fig. 4).

The mouse chromosomal location of *Taci* was determined by interspecific backcross analysis with progeny derived from matings of [(C57BL/6J × *Mus spretus*)F_1 × C57BL/6J] mice. This interspecific backcross mapping panel has been typed for over 2900 loci that are well distributed among all the autosomes as well as the X Chr (Copeland and Jenkins 1991). C57BL/6J and *M. spretus* DNAs were digested with several enzymes and analyzed by Southern blot hybridization for informative restriction fragment length polymorphisms (RFLPs) with a mouse genomic DNA probe. The 1.0-kb *Hin*cII *M. spretus* RFLP (see Materials and methods) was used to follow the segregation of the *Taci* locus in backcross mice. The mapping results indicated that *Taci* is located in the central region of mouse Chr 11 linked to *Il13*, *Kcnj2*, and *Myhsf1*. Although 93 mice were analyzed for every marker and are shown in the segregation analysis (Fig. 5), up to 174 mice were typed for some pairs of markers. Each locus was analyzed in pairwise combinations for recombination frequencies using the additional data. The ratios of the total number of mice exhibiting recombinant chromosomes to the total number of mice analyzed for each pair of loci and the most likely gene order are: centromere–*Il13*–4/146—*Kcnj2*–0/174–*Taci*–3/124–*Myhsf1*. The recombination frequencies [expressed as genetic distances in centiMorgans (cM) ± the standard error] are–*Il13*–2.7 ± 1.4–[*Kcnj2*, *Taci*]–2.4 ± 1.4–*Myhsf1*. No recombinants were detected between *Kcnj2* and *Taci* in 174 animals typed in common, suggesting that the two loci are within 1.7 cM of each other (upper 95% confidence limit).

We have compared our interspecific map of Chr 11 with a composite mouse linkage map that reports the map location of many uncloned mouse mutations (provided from Mouse Genome Database, a computerized database maintained at The Jackson Laboratory, Bar Harbor, Me.). *Taci* mapped in a region of the

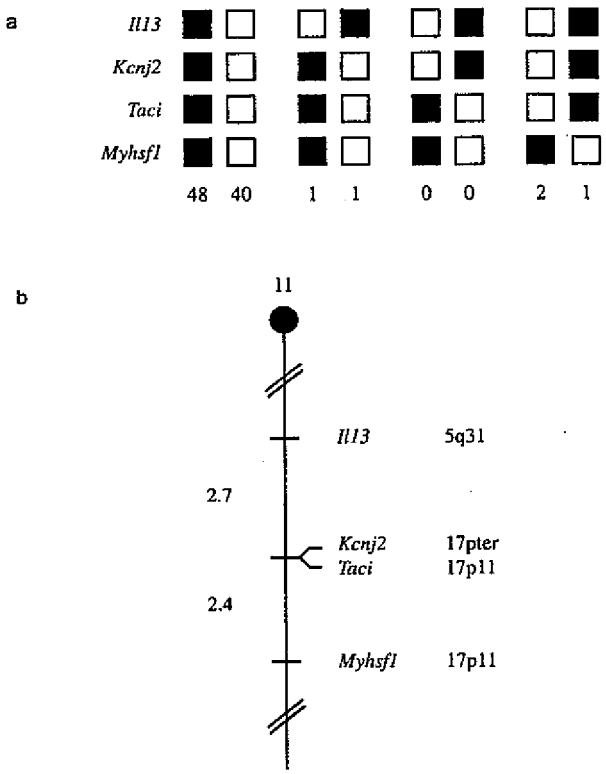


Fig. 5. *Taci* maps in the central region of mouse Chr 11. Taci was placed on mouse Chr 11 by interspecific backcross analysis. (a) Segregation patterns of Taci and flanking genes in 93 backcross animals that were typed for all loci. For individual pairs of loci, more than 93 animals were typed (see text). Each column represents the chromosome identified in the backcross progeny that was inherited from the (C57BL/6J × *M. spretus*) F_1 parent. The shaded boxes represent the presence of a C57BL/6J allele, and white boxes represent the presence of an *M. spretus* allele. The number of offspring inheriting each type of chromosome is listed at the bottom of each column. (b) A partial Chr 11 linkage map showing the location of *Taci* in relation to linked genes. Recombination distances between loci in centiMorgans are shown to the left of the chromosome, and the positions of loci in human chromosomes, where known, are shown to the right. References for the human map positions of loci cited in this study can be obtained from GDB (Genome Data Base), a computerized database of human linkage information maintained by The William H. Welch Medical Library of The Johns Hopkins University (Baltimore, Md.).

composite map that lacks mouse mutations with a phenotype that might be expected for an alteration in this locus (data not shown).

The central region of mouse Chr 11 shares regions of homology with human Chr 5q and 17p (summarized in Fig. 5). Thus, the mapping of *Taci* to 17p11 confirms and extends the homology between mouse 11 and human 17p.

To date, no immunological defects in either human or mouse have been mapped to the regions occupied by the *Taci* locus. The short arm of human Chr 17 is, however, a common target for mutation or rearrangement (the locus for tumor protein P53 is 17p13), leaving open a possible role for TACI in human disease. The molecular cloning of murine TACI and comparison with its human homology identify potentially important regions of the proteins which will be a useful guide to future studies. In particular, the nature of type III transmembrane proteins, the residues of the TNFR portions which make up the conserved cystine-rich domains, and possible cytoplasmic domains important in intracellular signal transduction. Cloning of the murine gene also paves the way for in vivo studies in mice by using transgenic technologies, potentially providing physiological data on the role of TACI in immune function.

Acknowledgments. We thank Virginia Valentine and Andreé Reuss for expert technical assistance. This research was supported, in part, by NCI grant 1R01CA76274, by the National Cancer Institute, DHHS, under contract with ABL, and by Joseph Bloom Childrens Disease Research. The accession numbers for human TACI are GDB:9834791, Genbank: AF023614. The sequence data for mouse TACI will be submitted to Genbank.

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